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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/983,474	06/30/1998	DAVID KLATZMANN	31649-134353	1470

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BASI, NIRMAL SINGH

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1646

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 08/983,474	Applicant(s) KLATZMAN et al
Examiner Nirmal S. Basi	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on Sep 12, 2001.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-18, 20, and 22-26 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 2, 3, 13-15, 22, 24, and 25 is/are allowed.
- 6) Claim(s) 1, 4-12, 16-18, 20, 23, and 26 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) All b) Some* c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892) 18) Interview Summary (PTO-413) Paper No(s). _____
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) Notice of Informal Patent Application (PTO-152)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) Other: _____

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DETAILED ACTION

1. Amendment filed 9/21/01 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (3/21/00, paper number 13).

5 **Claim Rejection, 35 U.S.C. 112, second paragraph,**

3. Claims 4-7, 9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, 9 and 11 are indefinite as it is not clear what are the “derived” polypeptide
10 fragments. “Derived has been considered, by Examiner, to be a derivative. Applicants arguments have been considered but not found persuasive. The term “derives” and “derivative” carries no weight in terms of structure and function and encompasses numerous alterations (modifications and mutations) and reads on unrelated proteins.

Claims 4 is indefinite as it is not clear what are proteins of the “CD type” so as to allow the
15 metes and bounds of the claim to be determined. The term “CD type” carries no weight in terms of structure and function and reads on unrelated proteins, the metes and bounds of which can not be determined based on prior art and the specification. It is not clear when a protein is of “CD type” as compared to when it is not of the “CD type”.

Claims 6 and 7 are rejected for depending on an indefinite base claim and fail to resolve the issues
20 raised above.

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Claim Rejections - 35 USC § 112, First Paragraph

4. Claim 18 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant multimeric protein, comprising a fusion polypeptide (linked by disulfide bridges) consisting of monomer A and monomer B of C4BP containing heterologous 5 polypeptides in relation to the alpha and beta chains, does not reasonably provide enablement for medicaments and their uses in therapy or prophylaxis of foetomaternal alloimmunization, viral, bacterial or parasitic infections, disseminated lupus erythematosus, or other alloimmune or autoimmune diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with 10 these claims. Applicant argues that Applicants have demonstrated high levels of drug in nude mice and similar levels can be expected in humans and this concentration retains the capacity to inhibit HIV infection. Applicants arguments have been fully considered but not found persuasive. The presence of high levels of drug in a system do not form the nexus of treatment prophylaxis of foetomaternal alloimmunization, viral, bacterial or parasitic infections, disseminated lupus 15 erythematosus, or other alloimmune or autoimmune diseases.

The specification lists many applications which the protein of the claimed invention might or might be expected to be useful for, including: immuno-intervention in human immune pathologies (page 3). The specification has not taught how to treat medical conditions requiring any of the above actions. Although the specification states the object of the present invention is to achieve 20 “immuno-intervention in the immune pathologies” (page 3, line 14-23), there is no disclosure of any

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results with the claimed fusion protein in assays, and the actual functional properties remain unknown. One skilled in the art cannot predict which fusion proteins might yield positive results. The effect of administration of the claimed fusion protein, which has no disclosed homology with other known proteins, for medical conditions is unpredictable. Furthermore, using said fusion 5 proteins for therapy or prophylaxis would require undue experimentation.

The unpredictability in the art is shown by Haynes (Ref. A, see paper number 13). Haynes states, "major scientific obstacles blocking the development of a successful preventative HIV vaccine are the extraordinary variability of HIV, the lack of an exact animal model or HIV-induced AIDS and the lack of understanding of the correlates of positive immunity to HIV", see abstract, page 39. 10 Further Haynes, states that, "Current animal model of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection(10). In some such models, such as the chimpanzee, animals do not develop AIDS. Other models lack immune responses analogous to human anti-HIV T and B-cell responses. Therefore many immunotherapeutic agents would be expected to be inactive in other species. In addition, owing to the extreme complexity of the host-tumor immuno-relationship, animal models do not fully mimic the biology of human patients with 15 cancer. Finally, the immune system is obviously different in humans and animals, and it is not surprising that immunotherapeutic agents fail to demonstrate comparable activity in animals and humans. For all these reasons it will be necessary to develop immunotherapy intended for humans in humans. Further the complexity of immune-based therapies in HIV infections and AIDS is 20 highlighted by Fahey et al. Fahey et al disclose, "Initial therapies aiming to alter immune function

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in patients with HIV infection have had mixed results", see abstract. Further disclosed are that soluble CD4, CD4-IgG, immune serum/gammaglobulin, murine MoAbs to gp120 core loop have all been unsuccessful for the effective therapy for viral infections, see RECEPTOR DIRECTED TREATMENT, page 3. Some of the *in vitro-in vivo* discrepancy may be explained in part by the 5 observation that viruses isolated from patients receiving, e.g. CD4 therapy, were 2 logs less sensitive than laboratory strains, page 3, column 1, second paragraph.. Also circulation through the liver and the kidney *in vivo* can reduce the persistence of therapeutic agents markedly, page 4, column 2, first paragraph. Further instant application claims fusion proteins, e.g containing antibodies, for treating various diseases but has not disclosed any specific constructs that may be effective in such 10 treatments. The epitope used to raise the antibody, nor the diseases they treat are not disclosed. Due to the large quantity of experimentation necessary to produce and isolate functional fusion polypeptides and the lack of direction/guidance presented in the specification regarding such polypeptides, the lack of working examples, the complex nature of the diseases claimed, e.g HIV infection, the unpredictability of the effects of immunotherapeutic agents in the treatment of such 15 disease, lack of animal models, as discussed above, and the breadth of the claims which claim therapy of a spectrum of diseases without disclosure of effective chimeric polypeptides for their successful treatment, undue experimentation would be required of the skilled artisan to make and /or use the claimed invention in its full scope.

5. Claims 4, 5, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the 20 specification, while being enabling for a recombinant multimeric protein comprising CD4, does not

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reasonably provide enablement for the claimed derived proteins. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

“Derived has been considered, by Examiner, to be a derivative. Applicants arguments have
5 been considered but not found persuasive. The term “derives” and “derivative” carries no weight in terms of structure and encompasses numerous alterations (modifications and mutations) and reads on unrelated proteins. Applicants arguments have been fully considered but not found persuasive.
10 Applicant has not disclosed which mutations would produce functional proteins and has not shown how to use those that are not functional. While the person of ordinary skill in the art would, in light of the specification be able to make recombinant multimeric proteins comprising fusions with CD4, the scope of the claims, which encompass other fusion proteins comprising derivatives without specific activity are not enabled by the disclosure. The disclosure does not teach how to make and purify and use functional derived proteins, and does not teach which alterations to CD4, for example, would result in functional fusion derivatives, or to use a commensurate number of said
15 fusion derivatives without functional activity. Further the disclosure does not disclose the structural limitations required to produce truncated fusion polypeptides of said derivatives. Instant specification does not teach which particular amino acids are critical for the active derivative. In other words, such structurally deficient derivatives containing random mutations would be expected by the skilled artisan to result in inactive proteins. For example, Rudinger (Ref C, see paper number
20 13) states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence.

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A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study".

5 Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for functional derivative, would prevent the skilled artisan from determining whether any modification or mutation to the CD4 molecule or other CD type molecules could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within said protein itself would be predicted to adversely alter
10 its biologically active 3-dimensional conformation, without undue experimentation to determine otherwise. Due to the large quantity of experimentation necessary to identify and purify active derivatives, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said derivatives, the unpredictability of the effects of mutation on the structure and function of CD4 other CD type molecule derivatives, disclosure on
15 how to use a commensurate number of derivatives lacking functional activity and the breadth of the claim which fail to recite functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

Claim Rejections, 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

20 basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5 Claims 1, 4-11,⁴15, 17, 20, 23 and 26 rejected under 35 U.S.C. 102(b) as being anticipated by Biogen Inc (IDS Ref AH). Biogen Inc. disclose a recombinant multimeric protein comprising the alpha chain of C4BP and the beta chain of C4BP wherein monomer are linked by disulfide bonds (pages 5-7, for example). Further disclosed are that the multimeric fusion polypeptide can conation fusions comprising immunoglobulins, antigens , CD4 type proteins and therapeutic enzymes (pages 10 9-31) , absent evident to the contrary. Also disclosed are host cells containing the recombinant polypeptide and methods of producing recombinant polypeptide Biogen Inc.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

20 Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Nirmal S. Basi
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November 19, 2000

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